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Autoimmune Neurogenic Dysphagia

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Abstract: ***Autoimmune neurogenic dysphagia is a kind of dysphagia caused by autoimmune diseases that affect the muscle, neuromuscular junction, nerves, roots, brainstem, or cortex. Dysphagia can be a part of a rising clinical symptomatology of an underlying neurological autoimmunity, or it might be a solitary, acute or insidious manifestation. This article describes the autoimmune neurological causes of dysphagia, the clinical signs & symptoms, laboratory testing that can help with early diagnosis, especially when dysphagia is the presenting complaint, and the most effective immunotherapeutic therapies. Dysphagia is prevalent in inflammatory myopathies, particularly inclusion body myositis, and it also occurs often in myasthenia gravis, appearing early in bulbar-onset sickness or later in progressive, generalised disease. Acute dysphagia is common in Guillain-Barre syndrome variations, while slowly progressing dysphagia is common in paraneoplastic neuropathies with particular autoantibodies. The most common causes of CNS autoimmune dysphagia are demyelinating and inflammatory lesions in the brainstem, which occur in persons with multiple sclerosis and neuromyelitis optica spectrum disorders. Dysphagia in stiff-person syndrome, particularly in connection with cerebellar ataxia and strong anti-GAD autoantibodies, and gastrointestinal dysmotility syndromes due to autoantibodies against the ganglionic acetylcholine receptor, are less common yet can be overlooked. In the setting of many CNS autoimmunities, acute-onset or growing dysphagia is a potentially curable condition that needs heightened vigilance for timely diagnosis and immunotherapeutic treatment.***

Keywords: Dysphagia, Deglutition, Deglutition disorders, Neurological autoimmunity, inflammatory myopathies, Myasthenia gravis, autoimmune neuropathies, Neuromyelitis, Stiff-person syndrome, Immunotherapies

1.Introduction

Dysphagia is a condition that manifests as difficulty in swallowing food or liquids and can range in severity from moderate to severe, affecting quality of life and potentially leading to life-threatening problems such as malnutrition, weight loss, and aspiration pneumonia. Swallowing is a complex skill that requires the coordination of skeletal and smooth muscles, as well as the involvement of the central, peripheral, and autonomic nervous systems (oral, pharyngeal, and esophageal). Despite the fact that dysphagia is most commonly caused by a local oropharyngeal or a wide, systemic medical illness, it can be completely caused by a neurological disease such as stroke, head injury, dementia, Parkinson's disease, cerebral palsy, or motor neuron disease (Amyotrophic Lateral Sclerosis). Dysphagia can be the first or sole symptom of an autoimmune neurological disorder, or it can appear as part of a wider range of symptoms as a result of a variety of CNS autoimmunities. Because dysphagia treatment is based on the underlying cause, identifying an autoimmune trigger or connection is critical, as immunotherapies can elicit reactions in people with autoimmune dysphagia. As a result, autoimmune neurogenic dysphagia is a critical and neglected illness that needs special care from all specialists. IgG4-related disease and eosinophilic esophagitis are gastroenterological causes of dysphagia; pemphigus vulgaris and bullous pemphigoid are dermatological causes; rheumatologic causes include scleroderma, Sjogren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, Behcet disease, Antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis, or granulomatosis with polyangiitis. In this article, we review the most successful immunotherapeutic therapies and review the autoimmune neurological causes of dysphagia. We emphasise clinical signs and laboratory tests that facilitate early diagnosis, particularly when dysphagia is the main symptom. We focus on inflammatory autoimmune myopathies, myasthenia gravis, autoimmune cranial neuropathies in the Guillain-Barre syndrome and multiple sclerosis spectrum as well as less common autoimmune neurological diseases like neuromyelitis optica, Stiff-person spectrum disorders, and ganglionic acetylcholine receptor autoantibody-related autoimmunities.

Epidemiology

This appears to afflict at least 30 % of Multiple sclerosis (MS) patients [1]. Furthermore, objective testing may uncover the issue in as many as 80% of instances [1, 2]. It emphasises the problem of underreporting this symptom, as well as the significance of a thorough clinical assessment and the use of more advanced diagnostic methods, particularly in high-risk situations [3]. However, there is a significant disparity between findings from various locations. According to a comprehensive study published in 2015, Iran had the lowest reported prevalence of dysphagia in MS, whereas Europe has the highest [1]. As expected, people with greater disability ratings and longer illness duration are more likely to have deglutition problems [1, 2, 4, 5]. It is, nevertheless, not uncommon in the early stages of the disease [5]. It might be minor and infrequent, or severe and incapacitating. At a Brazilian research, 90 % of 108 MS patients had dysphagia in various phases. The majority of the cases were of a mild to moderate difficulty. About 12.5 % of those with severe dysphagia were in advanced stages of MS and had a higher expanded disability status scale (EDSS) [2].

Pathophysiology

Lesions of the brainstem and cerebellum appear to be more linked to dysphagia [4, 6]. It's more likely that the

pharyngeal phase will be engaged [4]. This might be due to a weakened gag reflex or a lack of coordination in muscular contractions [3]. We may list cranial neuralgias and facial paresis as examples of additional disorders that make swallowing difficult. In Multiple sclerosis (MS) trigeminal, glossopharyngeal, or occipital neuralgias may occur. Depending on the affected location, these unpleasant electric-shock-like episodes may modify easy swallowing in different phases. Disturbed sensations might make the task much more difficult. Another interfering issue might be facial paresis. It might lead to insufficient chewing, making the bolus difficult to swallow. Furthermore, cognitive impairment may exacerbate the difficulty.

Autoimmune Neurological Disorders with Dysphagia

As the earliest symptom of an autoimmune process or over the course of a progressive neurological autoimmune illness, autoimmune neurogenic dysphagia can be seen with disorders affecting muscle, neuromuscular junction, cranial nerves, brainstem, or corticospinal CNS systems. Inflammatory myopathies, neuromuscular junction disorders, autoimmune cranial neuropathies, autoimmune ganglionopathies or dysautonomic disorders and autoimmune central nervous system diseases are among the most prevalent disorders in this category, which are listed in Table 1 with anatomic sequence.

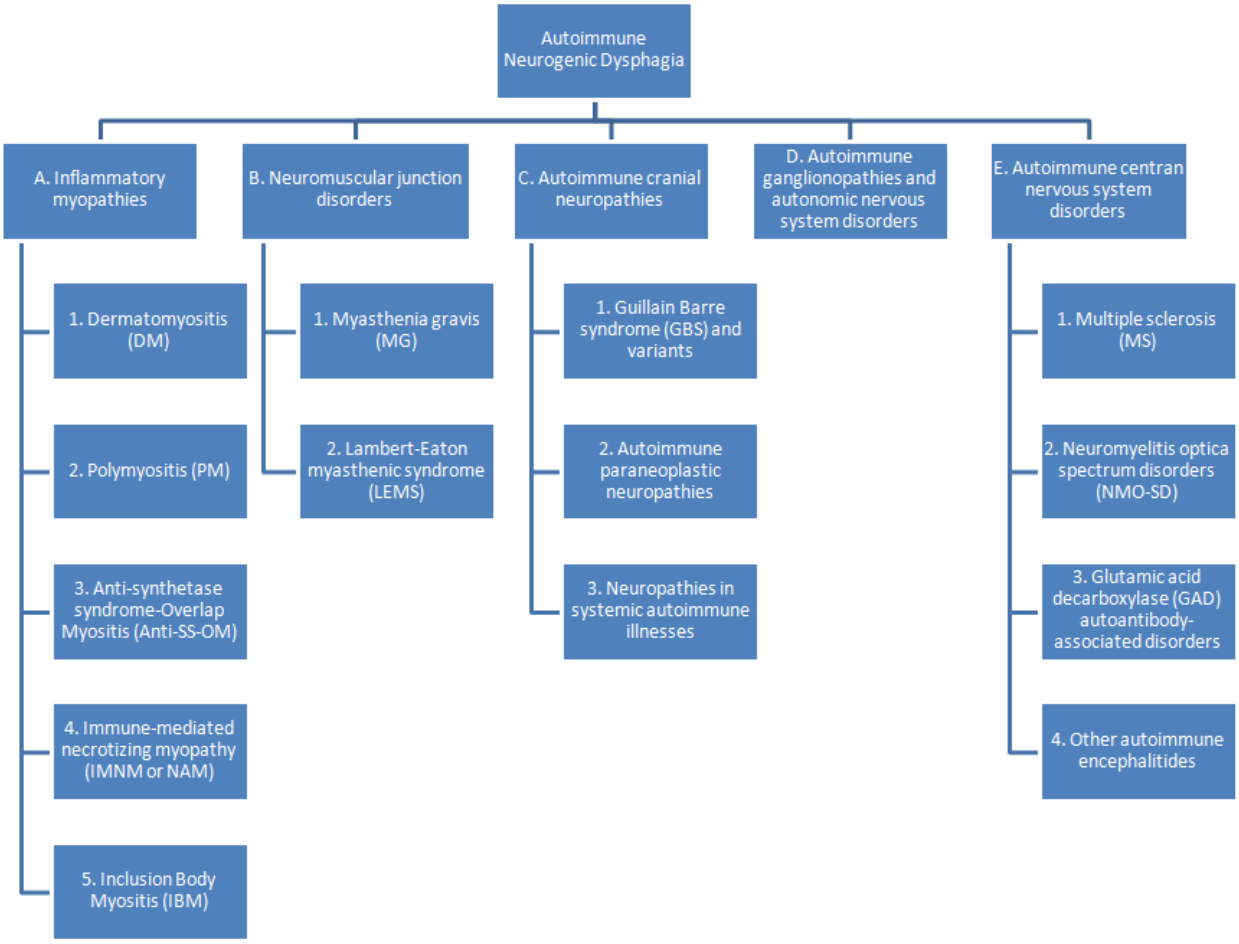

Table 1: Autoimmune neurological disorder with dysphagia

A) Inflammatory Myopathies

Polymyositis (PM), dermatomyositis (DM), and inclusion body myositis (IBM) were originally classified as inflammatory myopathies [7, 8], but have since evolved to include immune-mediated necrotizing myositis (IMNM) or necrotizing autoimmune myositis (NAM), as well as anti-synthetase syndrome-overlap myositis (Anti-SS-OM) [9, 10] Dysphagia occurs in all subtypes, however it is most common in IBM, followed by Anti-SS-OM, DM, and NAM in our experience. Despite the diversity of inflammatory myopathies, few studies have looked at dysphagia prevalence in pooled cohorts of distinct disease subgroups. Dysphagia was reported in 36% of individuals with inflammatory myopathy in a meta-analysis involving 116 studies and 10, 382 people [11]. The frequencies of dysphagia increased to 82 % when only trials with minimal probability of bias were included, highlighting the need of a high degree of suspicion in early detection. The diagnosis of IBM, an underlying malignancy, or a suspected malignancy, as in DM patients with anti-nuclear matrix protein 2 (NXP2) antibodies, were all risk factors for dysphagia [11]. According to a retrospective chart-review research, 23 % of 230 DM/PM patients had dysphagia at the time of diagnosis, but 58 % acquired dysphagia as the disease progressed [12]. Dysphagia was reported in 10% of participants in a second, smaller, retrospective, questionnaire-based investigation of 50 patients (35 with DM and 8 with PM) [13]. Studies that focus on particular inflammatory myopathy subgroups, as

stated below, give more insight into the prevalence of dysphagia at illness initiation or over the course of the disease. Dysphagia occurs over the course of the disease, not at presentation, in our experience with many inflammatory myopathy patients, with the exception of IBM, when it can be an early sign causing diagnostic problems.

1) Dermatomyositis

Dermatomyositis (DM) affects both children and adults and is characterised by cutaneous symptoms that precede or accompany muscular weakening. Typical skin lesions include periorbital heliotrope (blue-purple) rash with edoema, erythematous rash on the face, knees, elbows, malleoli, neck, anterior chest (in V-sign), back and shoulders (in shawl sign), and knuckles with violaceous eruption (Gottron's rash) that evolves into a scaling discoloration. Muscle histology reveals inflammation mostly perivascularly, in the interfascicular septae or at the fascicle's periphery, with perifascicular atrophy and capillary abnormalities [8]. Early complement activation with the C5b-9 membranolytic-attack complex deposited on endothelial cells causes capillary necrosis, endomysial capillary shrinkage, ischemia, and muscle fibre damage that resembles microinfarcts in DM [7-9]. Autoantibodies to MDA5, anti-TIF1-gamma, anti-NXP2, and anti-small ubiquitin-like modifier-activating enzyme (anti-SAE) have also been found. Anti-NXP2, which frequently indicates an underlying malignancy, has been linked to dysphagia [14]. In all, around 15% of DM patients may have an underlying cancer. Dermatomyositis can occur in the presence of various systemic autoimmunities, the most common of which is systemic sclerosis, which is linked to dysphagia owing to esophageal fibrosis [15]. Dysphagia in DM varies from 31% (N = 3274) in a heterogeneous meta-analysis to 43% (N = 949) in the Euromyositis registry, and even more than 60% (N = 117) in a cohesive retrospective cohort [11, 12, 16]. Dysphagia was seldom the presenting symptom of DM in a more targeted retrospective analysis of patients with inflammatory myopathies and dysphagia that additionally included video-fluoroscopic swallow tests (VFSS) [17, 18], which is similar with our own findings in large series. Dysphagia was linked to an increased risk of death in one of those studies, with 5 of 18 dysphagic patients dying within the first year of follow-up; however, this study is not representative because a number of these patients had cancer and no information on early diagnosis or immunotherapy initiation was provided [17]. The appearance of the typical skin lesions commonly linked with elevated creatine kinase (CK) levels should raise disease concern. Muscle biopsy is used to confirm the diagnosis. Early in the illness, high-dose steroids and steroid-sparing medications (particularly methotrexate, azathioprine, or mycophenolate) are beneficial. High-dose intravenous immunoglobulin (IVIg) is the therapy of choice in individuals who are not responding well [19]. Based on a 20-item neuromuscular symptom score that included dysphagia, IVIg had a profound effect on patients' proximal muscle strength and neuromuscular activity in the sole controlled research [19]. Because DM is a complement-mediated microangiopathy, suppression of complement activation and interception of the membranolytic-attack complex on endothelial cells, restoring the integrity and population of endomysial capillaries, is immunopathologically supported by IVIg [20]. If IVIg isn't successful enough, rituximab is started. Additional advantages may be obtained through rehabilitation and compensatory strategies (e.g., a particular diet, feeding methods such as tiny bites and alternating solids and liquids, and exercises such as tongue base retraction and effortful swallowing) [17]. Percutaneous endoscopic gastrostomy (PEG) may be necessary in severe early instances to prevent aspiration pneumonia and malnutrition until the aforementioned immunotherapies take action, which usually takes 2-3 months. The use of PEG for an extended period of time causes significant atrophy of the pharyngeal and laryngeal muscles, making it more difficult to return to normality.

2) Polymyositis

Polymyositis (PM) is a rather uncommon condition. Most patients who are referred for PM have another muscle illness, most often IBM, NAM, or an inflammatory dystrophy, in our experience. According to a older studies, dysphagia affects 35 % to 50 % of PM patients [11, 12, 16], but these figures should be interpreted with caution because these figures are unlikely to refer to PM; they do, however, reflect the fact that dysphagia is a common symptom in inflammatory myopathies.

3) Anti-Synthetase Syndrome-Overlap Myositis (Anti-SS-OM)

Overlap of anti-synthetase syndromes Systemic sclerosis-like lesions, mild-to-moderate proximal muscle weakness, arthritis in the form of dislocation of the interphalangeal joints, "mechanic's hands, " Raynaud phenomenon, and interstitial lung disease are all common symptoms of myositis (Anti-SS-OM). [9] The presence of anti-aminoacyl transfer RNA synthetase autoantibodies, mainly anti-Jo-1, distinguishes the disease, thus the term "anti-Jo-1 syndrome." Muscle biopsies from these individuals revealed necrotizing characteristics in the perimysium and perifascicular muscle fibres [9, 10]. Dysphagia is widespread (found in 26% of anti-SS-OM patients in the Euromyositis registry [16]), however it is mild to moderate in severity compared to the other inflammatory myopathy categories. Dysphagia was the major presenting symptom in one of nine anti-SS-OM patients in a retrospective investigation of patients with inflammatory myopathies and dysphagia, which included VFSS in about half of the patients [17]. Immunotherapy for dysphagia is the same in anti-SS-OM as it is in DM. Dysphagia anti-SS-OM patients react to treatments considerably better and quicker than DM patients, according to our experience; this is also supported by 5-year survival statistics from nine anti-SS-OM patients with dysphagia as their primary symptom [17].

4) Immune-Mediated Necrotizing Myopathy (IMNM or NAM)

Immune-mediated necrotizing myopathy (IMNM), also known as necrotizing autoimmune myositis (NAM), is currently the most frequent inflammatory myopathy in people of all ages [9]. It can begin acutely, peaking over days or weeks, or subacutely, advancing slowly and causing severe muscular weakness, dysphagia, and very high (thousands) CK levels [9]. NAM can also arise as a result of viral infections, as well as in the presence of malignancy or immune checkpoint inhibitors. Despite the fact that subacute NAM is frequently attributed to statins or misdiagnosed as a "statin-myopathy" in patients on long-term statin therapy, there is no convincing evidence that statins play a triggering role in patients who develop subacute NAM while on long-term statin therapy [7, 20-22]. Since NAM is currently the most frequent inflammatory myopathy and over 25% of Americans over 40 take statins, the link between statins and NAM is most likely coincidental [21, 22]. Antibodies to signal recognition particle (SRP) or 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), a ubiquitous and non-muscle-specific antigen inside the endoplasmic reticulum that is more commonly observed in NAM patients with cancer, are found in the majority of NAM patients. In the Euromyositis registry, dysphagia was seen in more than 30% of NAM patients (total N = 3067, NAM N = 107) [17]. Only one of four patients with early or prominent dysphagia triggered by immune checkpoint inhibitors (ICPI) had cricopharyngeal prominence on VFSS, but all had impaired pharyngeal contraction and three had impaired tongue base retraction and epiglottic inversion/laryngeal elevation with aspiration; concurrent ophthalmoparesis was also noted, as is common in ICPI-triggered NAM [18]. Most NAM patients, even those with severe illness, respond to immunotherapy with intravenous corticosteroids in the initial phase, followed by IVIg and, if necessary, rituximab, according to our experience.

5) Inclusion Body Myositis (IBM)

Inclusion Body Myositis (IBM) is the most prevalent and debilitating inflammatory myopathy in those over 50 [7-9], as well as the most common cause of inflammatory myopathy-related dysphagia. It begins gradually over years, often asymmetrically, and proceeds steadily, mimicking late-life muscular dystrophy or a slowly advancing motor neuron disease that results in substantial impairment [7-9]. Although early involvement of distal muscles, especially foot extensors and finger flexors, atrophy of the forearms and quadriceps muscles, dysphagia, frequent falls due to quadriceps muscle weakness causing buckling of the knees, and mild facial muscle weakness are clues to early clinical diagnosis [7-9], early involvement of distal muscles, especially foot extensors and finger flexors, atrophy of the forearms and quadriceps Muscle biopsy reveals inflammatory infiltrates comprised mostly of CD8+ cytotoxic T-cells invading muscle fibres expressing MHC-I antigen, as well as autophagic vacuoles with congophilic amyloid deposits, confirming the diagnosis based on the specific clinical pattern [7-9]. Antibodies to cytosolic 5-nucleotidase 1A (cN1A) are found in 50% of patients, however they are not specific. IBM is associated with dysphagia, which is more common than any other inflammatory myopathy [23-30]. The Euromyositis registry reported a cumulative dysphagia prevalence of up to 50% and a meta-analysis reported a prevalence of 56 % [11, 16], but these investigations were diverse and lacking in clinical information. Dysphagia was the lone presenting symptom or one of the primary presenting symptoms in 10% of IBM patients in numerous single-center studies with solid data [18, 28, 29], with the incidence rising to 40% at the time of diagnosis [25]. VFSS demonstrated symptoms of poor propulsion in 77 % (repetitive swallowing 25 %, residues 36 %, and cricopharyngeal dysfunction 16 %) and aspiration-related signals (mainly insufficient epiglottal downward tilting) in 53 % (N = 43) of IBM patients [25, 26]. 15 patients with IBM were studied with VFSS in a study of myopathies with early or prominent dysphagia [18]; impaired pharyngeal contraction was noted in 9, impaired tongue base retraction in 10 and epiglottic inversion/laryngeal elevation in 8, with the pharyngeal phase more severely affected than the oral phase; aspiration was observed in three patients during the study [18]. Pharyngeal pooling was detected in 85 % of IBM patients tested with VFSS, as was impaired tongue base retraction in 76 %, and impaired laryngeal elevation in 50 %; aspiration was reported in 26 % of the patients [17]. Dysphagia was detected in 80 % of the 15 survivors in a survey of 64 IBM patients followed for a median of 12 years. The prevalence of cricopharyngeal sphincter dysfunction/bar (potentially treatable) varied from 42 % on barium swallow [25] to 37-47 % on VFSS [17, 23, 24]. Not unexpectedly, research on dysphagia found that IBM was present in the majority of individuals with all inflammatory myopathies [17, 18]. Isolated dysphagia, for example, can be the main symptom of IBM [29] or one of the presenting symptoms in 42% of individuals [17]. Progressive dysphagia in IBM, in our view, is a marker of more severe illness, as others have recently verified [18].

Based on a controlled trial [27], IVIg is the only proven medication that may partially alleviate dysphagia in some IBM patients. IVIg did not enhance muscular strength in this trial, but it did improve swallowing, as measured by VFSS paired with a sensitive quantitative ultrasonography approach that objectively assesses the mean time (in seconds) needed to complete three dry and three wet swallows [27]. All immunosuppressive drugs tried in IBM failed, owing to the fact that the illness begins years before individuals seek medical help. Glucocorticoids, methotrexate, cyclosporine, azathioprine, and mycophenolate are all useless, and while some patients may see little improvements at first, there is no long-term benefit. In an uncontrolled experiment, alemtuzumab which is a B and T cell-depleting anti-CD52 monoclonal antibody, showed encouraging benefits [31], but canakinumab, an anti-IL-1 monoclonal antibody, gave mixed results in a limited trial of 5 patients [32]. Anakinra, an IL-1 receptor blocker, has also showed moderate short-term benefits in a subgroup of patients in the initial series [33] and 15 patients in a later research [34]. Because a cricopharyngeal bar is frequent, invasive treatments such as balloon dilatation and myotomy can relieve symptoms

and contribute to weight loss in individuals with severe dysphagia prior to PEG implantation [26, 35-39], albeit this benefit was not long lasting after 5 years [23]. Botox injections have not shown to be effective in our experience. The Mendelsohn manoeuvre (conscious prolonging of peak-swallow laryngeal elevation) has demonstrated some efficacy in terms of rehabilitation procedures [36]. Overall, while life expectancy appears to be unchanged, most IBM patients with end-stage illness require assistance equipment such as a cane, walker, or wheelchair [40]; dysphagia is the greatest life-threatening symptom in those patients who do not react to IVIg.

B) Neuromuscular Junction Disorders

Myasthenia gravis (MG) is a kind of autoimmune illness that causes muscular weakness in the skeletal, bulbar, and respiratory muscles, as well as tiredness from repetitive movements or muscle motions and difficulty chewing or swallowing [41]. Autoantibodies against nicotinic acetylcholine receptors (AChR) cause MG symptoms and pathology, which are seen in 85 % of patients. The AChR antibodies bind to complement in the end-plate area, causing the AChRs to be destroyed and the endplates to be simplified. Anti-AChR antibodies are not found in 15% of patients; of those, 50%, or 5-8% of all AChR-negative MG cases, are positive for antibodies against muscle-specific kinase (MuSK), a transmembrane polypeptide produced at the neuromuscular junction that plays a key role in AChR clustering [42]. Anti-MuSK antibodies belong to the IgG4 subclass and are non-complement binding in most cases. MG can have an early or late start, and symptoms might be restricted to extraocular muscles (ptosis, diplopia), or they can become widespread, affecting all muscle groups. Bulbar symptoms such as dysphagia, dysphonia, dysarthria, and difficulties chewing are prevalent in MuSK-MG [43], with dysphagia being more common than in AChR-MG [44]. Dysphagia in MG (as in all cases of neurogenic dysphagia) is characterised by difficulty swallowing solids and liquids, and is caused primarily by pharyngeal and laryngeal muscle weakness and fatigue, and secondarily by esophageal hypomotility [45, 46]; the latter is confirmed by esophageal manometry, which reveals decreased amplitude of upper esophageal sphincter contractions and esophageal peristaltic waves [47] Mastication muscles can be affected by weakness and tiredness, making chewing difficult. Dysphagia is frequently associated with additional bulbar symptoms such as dysphonia and dysarthria, ocular signs such as ptosis and diplopia, and axial or neck muscular weakness in patients with MG [43, 48]. Clinically diagnosed dysphagia was evident at illness beginning in 25% of 84 MG patients in a large prospective study [49]. Clinically evaluated dysphagia was the major symptom in 15% of 175 MG patients who primarily presented with head and neck symptoms, and the secondary symptom in 12% [50]. Dysphagia can also be a part of the clinical syndrome in another autoimmune neuromuscular junction disorder, Lambert-Eaton Myasthenic Syndrome (LEMS), which is associated with antibodies against P/Q type voltage-gated calcium channels (VGCC) at presynaptic nerve terminals in about 50-75 % of patients and can be paraneoplastic in about 50-75 % of patients [51]. The presence of serum AChR or MuSK autoantibodies is used to confirm the diagnosis of MG. Single-fiber EMG or repeated nerve stimulation investigations are used to confirm the diagnosis in the 7% of seronegative MG patients who have fatigued weakness. When advanced, dysphagia caused by seronegative MG should be separated from ALS, which is accompanied by tongue atrophy. Electromyographic testing confirms the diagnosis, but if you're still not sure, a trial of oral pyridostigmine 60 mg QID will assist. Because MG is now a curable condition, identifying MG-related dysphagia is clinically beneficial for doctors and patients [52-54]. After ruling out thymoma, which affects 10% of AChR-MG patients, the AChR-positive MG patients are treated with pyridostigmine (an acetyl-cholinesterase inhibitor), steroids, and a steroid-free immunosuppressant such azathioprine or, more recently, mycophenolate. IVIg and plasmapheresis are effective in challenging instances or when dysphagia is combined with respiratory issues [55]. Rituximab, an anti-CD20 + monoclonal antibody that causes B-cell depletion, is similarly successful in the chronic therapy of refractory patients [52, 53]. Rituximab is a recommended therapy in MuSK-MG, where the antibodies are of the IgG4 subclass, even early in the illness course, leading to excellent long-term remission. It's critical to figure out if dysphagia is caused by a certain MG subtype early on, when symptoms first appear, because in the vast majority of cases, it's a curable illness with the right drugs. In addition to the mentioned medications, novel treatments for severe or refractory MG, such as eculizumab, a monoclonal antibody targeting complement C5, have recently received FDA approval. Another novel drug targeting the neonatal Fc receptor (FcRn), which boosts the catabolism of circulating IgG antibodies, has shown promise in phase III studies and is awaiting FDA approval [52].

1) Myasthenia gravis (MG)

A chronic neuromuscular condition called myasthenia gravis (MG) causes variable degrees of skeletal muscle weakening. [56] The muscles that control the eyes , face, and swallowing are most frequently impacted. [56] It may lead to difficulties walking, talking, or seeing well, as well as drooping eyelids. [56] Onset may occur quickly. [56] Those who are afflicted frequently grow a thymoma or have a big thymus. [56] Antibodies that block or kill nicotinic acetylcholine receptors (AChR) at the junction of the nerve and muscle cause myasthenia gravis, an autoimmune illness of the neuro-muscular junction. [57, 58, 56] As a result, neural impulses cannot cause muscular contractions. [56] Immunoglobulin G1 (IgG1) and IgG3 antibodies, which assault AChR in the postsynaptic membrane and result in complement-mediated damage and muscular weakening, are to blame for the majority of cases. [59] Rarely, a disorder known as congenital myasthenia is caused by an inherited genetic abnormality in the neuromuscular junction. [60, 61] Neonatal myasthenia refers to the symptoms that newborns of myasthenic mothers may have in the first few months of life. [56] Blood testing for certain antibodies, the edrophonium test, or a nerve conduction examination can all help confirm a diagnosis. [56] Acetylcholinesterase inhibitors, such as neostigmine and pyridostigmine, are

typically used to treat MG. Prednisone and azathioprine are two examples of immunosuppressants that can be employed. [56] In some circumstances, the surgical excision of the thymus may help symptoms. [56] During rapid flare-ups of the disease, plasmapheresis and high-dose intravenous immunoglobulin may be employed. [56] Mechanical ventilation could be necessary if the breathing muscles start to weaken severely. [56] Acetylcholinesterase inhibitors may be temporarily withheld after intubation to lessen airway secretions. 50 to 200 per million persons are affected by MG. [62] Every year, three to thirty per million persons receive a new diagnosis. As awareness has grown, diagnoses have become increasingly frequent. Men over the age of 60 and women under the age of 40 are most likely to get MG. [56] Children seldom experience it. [56] Most afflicted people have mostly normal lives and have a normal life expectancy after receiving therapy. [56] The name derives from the Greek words mys, meaning "muscle, " astheneia, meaning "weakness, " and gravis, meaning "serious." When a person is diagnosed with MG, their neurological condition is evaluated, and the severity of their sickness is determined. The standard Myasthenia Gravis Foundation of America Clinical Classification scale (Table 2) [63] is typically used for this.

Class	Description
I	Any eye muscle weakness, possible ptosis, no other evidence of muscle weakness elsewhere
II	Eye muscle weakness of any severity, mild weakness of other muscles
IIa	Predominantly limb or axial muscles
IIb	Predominantly bulbar and/or respiratory muscles
III	Eye muscle weakness of any severity, moderate weakness of other muscles
IIIa	Predominantly limb or axial muscles
IIIb	Predominantly bulbar and/or respiratory muscles
IV	Eye muscle weakness of any severity, severe weakness of other muscles
Iva	Predominantly limb or axial muscles
IVb	Predominantly bulbar and/or respiratory muscles
V	Intubation needed to maintain airway

Table 2: Myasthenia Gravis Foundation of America Clinical Classification [63]

2) Lambert - Eaton myasthenic syndrome (LEMS)

It is an uncommon autoimmune condition marked by limb muscle weakening. LEMS is recognised as a paraneoplastic syndrome since it is associated with an underlying malignancy in around 60% of patients who have it, most frequently small-cell lung cancer [64]. Antibodies against presynaptic voltage-gated calcium channels and maybe other proteins of the nerve terminals in the neuromuscular junction are to blame (the connection between nerves and the muscle that they supply) [65]. Electromyography and blood tests are typically used to confirm the diagnosis and to differentiate it from a comparable autoimmune neuromuscular condition called myasthenia gravis. [65] When cancer and the condition are directly treated, LEMS symptoms are frequently relieved. Steroids, azathioprine, which suppresses the immune system, intravenous immunoglobulin, which competes with autoreactive antibodies for Fc receptors, pyridostigmine, and 3, 4-diaminopyridine, which improve neuromuscular transmission, are other therapies that are frequently utilised. Plasma exchange may occasionally be necessary to get rid of the antibodies. [65] About 3.4 per million persons are affected by this disease. [56] Although it can happen at any age, LEMS often affects adults over the age of 40.

C) Autoimmune Cranial Neuropathies

Dysphagia can be caused by autoimmune cranial neuropathies alone or in combination with other symptoms caused by the same or nearby nerves. Horizontal binocular diplopia (cranial nerve VI), facial paralysis, and dysarthria (cranial nerve VII), hearing loss, balance problems, vertigo, and tinnitus (cranial nerve VIII), impaired taste and sensation in the posterior tongue and palate (cranial nerve IX), nasal voice/hoarseness (cranial nerve X), trapezius and sternocleidomastoid paresis (cranial nerve XI), and dysarth (cranial nerve XII). The pathomechanism of dysphagia in cranial neuropathies is aberrant signal conduction to the swallowing muscles, especially affecting the pharyngeal and laryngeal muscle groups (innervated by cranial nerves IX-X), resulting in liquid and solid dysphagia. The oral phase of swallowing is further aided by cranial nerves XII, which innervates the tongue muscles, cranial nerve VII, which innervates the lip muscles, and cranial nerve V, which innervates the mastication muscles. The cranial nerve X, which transmits autonomic fibres to the gastrointestinal system and controls esophageal motility, is particularly important. The following are the most frequent autoimmune/inflammatory neurological illnesses that impact cranial nerves and cause dysphagia.

1)Guillain-Barre Syndrome (GBS) and Its Variants

Guillain-Barre syndrome (GBS) is a monophasic autoimmune polyradiculoneuropathy that appears abruptly or subacutely and is commonly postinfectious (in less than 4 weeks). GBS is usually characterised by ascending weakness, but in Miller Fisher syndrome (MFS) and the pharyngeal-cervical-brachial (PCB) form, the cranial and cervical nerves are the primary targets. The MFS form is characterised by ataxia, ophthalmoplegia, and areflexia, whereas the PCB version is characterised by cervicobrachial and oropharyngeal weakness, as well as dysphagia [66-68]. GBS, PCB, and MFS, as well as Bickerstaff's encephalitis, are all thought to be part of the same illness [67-69], with dysphagia being a presenting symptom in certain instances [70]. MFS is related with anti-GQ1b antiganglioside autoantibodies, whereas PCB is associated with anti-GT1a antiganglioside autoantibodies with considerable cross-reactivity [67, 68, 71]. Clinical dysphagia was found in 88 % of eight individuals with anti-GT1a antibodies [72]. Clinical dysphagia is seen in 41 % (N = 54, [72]) to 53.5 % (N = 71, [73]) of GBS patients, with a greater frequency (75 %, N = 16) among ICU patients [74]. When the VFSS was used to assess dysphagia in 14 GBS patients who had been referred for swallowing evaluation, abnormalities were found in all of them, with the pharyngeal swallowing phase being more

severely affected than the oral phase. Of these 14 patients, six had equal involvement of the oral and pharyngeal phases, seven had more severe pharyngeal phase involvement, and one had more severe oral phase involvement. [75] Electrophysiological swallow investigations demonstrated silent dysphagia in 28% of non-ICU hospitalised GBS patients, whereas clinically overt dysphagia was seen in 38% of those patients [76]. These findings suggest that doctors should be cautious when placing a nasogastric tube in GBS patients and maintain a low threshold for doing so. The presence of areflexia on examination, high protein in an acellular CSF, potential nerve root enhancement on MRI, and symptoms of neuropathy (mainly demyelinating, but occasionally axonal) on EMG all aid in the diagnosis of GBS, MFS, and PCB. IVIg and PLEX are both equally efficacious and should be started as soon as possible [77, 78], therefore prompt diagnosis is critical. Dysphagia is uncommon in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), which is the chronic counterpart of GBS and has a subacute onset or a relapsing course [79, 80]. If it does occur, it responds to immunotherapy with IVIg, steroids, or rituximab in the same way as the other symptoms.

2) Autoimmune Paraneoplastic Neuropathies

Immunological repercussions of malignant tumours targeting nerves, especially those essential for swallowing, produce autoimmune paraneoplastic neuropathies. They should be separated from tumor-induced infiltration of the cranial nerves, such as lymphoma [81, 82], as well as chemotherapy or radiation-induced neuropathies. Immune checkpoint inhibitors, which abnormally activate the immune system and cause numerous immunological syndromes affecting nerve, muscle, neuromuscular junction, and brain, can also generate autoimmune neuropathies in cancer patients [82, 83]. The presence of autoantibodies is usually, but not always, indicative of the autoimmune process [84, 85]. Although uncommon, paraneoplastic autoimmune neuropathies that produce dysphagia are crucial to notice not only because they can occur before a tumour is diagnosed, but also because they can respond to immunotherapy and tumour excision. [84, 86, 87] Anti-Hu (antineuronal nuclear antibody-1) and anti-Ri (antineuronal nuclear antibody-2) antibodies in patients with small cell lung cancer [88, 89] may be indications of paraneoplastic neuropathy with more significant dysphagia [90]. Clinical dysphagia was seen in seven of 34 patients with Ri autoantibodies, along with polyradiculoneuropathy, brainstem, and cerebellar dysfunction or encephalopathy [90]. Tumor excision and immunotherapy are the first steps in treating paraneoplastic autoimmune neuropathies. Anti-Hu syndrome, in particular, can be aggressive and resistant to immunotherapies; however cyclophosphamide has shown to be effective in certain patients [86].

3) Neuropathies in Systemic Autoimmune Illness

Sarcoidosis is a systemic illness with significant cranial neuropathies, which constitute the presenting symptom in 5-10% of patients [91]. The facial nerve (VII) is the most prevalent cranial neuropathy in sarcoidosis; however other nerves such as the IX and X can also be damaged, leading in dysphagia. Dysphagia can also be caused by the involvement of other organs, such as the oesophagus [92, 93] and the swallowing muscular apparatus [94]. Increased circulating ACE levels, chest CT showing hilar lymphadenopathy, brain MRI showing leptomeningeal enhancement, PET-CT showing active inflammation sites, lumbar puncture revealing high protein and oligoclonal bands, and finally biopsy of accessible tissue showing non-caseating granulomas all aid in the diagnosis. Sarcoidosis is commonly treated with corticosteroids and steroid-sparing medicines like mycophenolate, as well as anti-TNF medications like infliximab and anti-CD20 agents like rituximab in more severe instances [92-94]. Sjogren's syndrome (SS) [95, 96], systemic lupus erythematosus (SLE) [97], and rheumatoid arthritis (RA) [98] can all cause neuropathy; dysphagia is more common in SS [99], despite the fact that it is sometimes mistakenly attributed to a lack of saliva and esophageal hypomotility rather than cranial nerve involvement [100].

D) Autoimmune Ganglionopathies and Autonomic Nervous System Disorders

An autoimmune reaction can occasionally target the dorsal root ganglia as well as autonomic nervous system components that govern the gastrointestinal tract [101]. Antibodies to the ganglionic AChR can cause such disorders, which are characterised by extensive dysautonomia, including gastrointestinal dysmotility and dysphagia (gAChR). Antibodies to Hu antigen or neuronal voltage-gated calcium channel (VGCC), mostly the N-type and to a lesser extent the P/Q type (also related with LEMS), can be found in cases with paraneoplastic association. Dysphagia can be produced directly by esophageal motility abnormalities, usually achalasia and occasionally widespread esophageal spasm, in the presence of gAChR and, to a lesser extent, VGCC autoantibodies [101, 102]. Once an autoimmune etiology has been determined, a search for an underlying neoplasia is necessary, followed by tumour resection and/or immunotherapy.

E) Autoimmune CNS Disorders

The anterior insula and the frontoparietal operculum are vital for swallowing, with corticobulbar fibres reaching the brainstem nuclei of cranial nerves V, VII, XII, IX, X engaged in the oral, pharyngeal, and esophageal stages of swallowing. The majority of instances of CNS dysphagia are caused by brainstem lesions, followed by insular and opercular lesions. Multiple sclerosis (MS), Neuromyelitis Optica Range Diseases (NMO-SD), hyperexcitability conditions within the stiff-person syndrome spectrum, and autoimmune encephalitis are all autoimmune CNS disorders that cause dysphagia.

1) Multiple Sclerosis (MS)

Dysphagia is more commonly encountered in primary or secondary progressive types of Multiple Sclerosis (MS), and it corresponds with the extended disability status scale

(EDSS), showing its link to advanced disease stages [103-105]. Dysphagia can occur in some acute MS cases when active demyelinating lesions impact the brainstem and in rare cases when active demyelinating lesions affect the operculum [106]. The prevalence of dysphagia ranged from 21 to 43 % in trials with more than 200 MS patients [106-113], when dysphagia was assessed clinically or by questionnaires. Dysphagia prevalence ranged from 54 to 90 % [114-117] in studies that used objective assessments like VFSS and fibre endoscopic swallow studies (FESS), indicating that MS clinicians should keep a low threshold for suspecting swallowing disturbances, especially in patients with progressive MS and high EDSS scores. A VFSS examination of 18 MS patients (10 with varied degrees of symptomatic dysphagia and 8 asymptomatic) revealed aspiration in all symptomatic patients with epiglottis undercoating and/or laryngeal penetration; the VFSS was also abnormal in 6 of the 8 asymptomatic individuals [116]. The clinical, radiographic, and CSF features of relapses or progression, as well as the elimination of other diagnoses, are used to diagnose MS [118, 119]. The probability of subsequent disability progression is reduced when patients get early immunotherapy with high-efficacy therapies [119, 120]. Rehabilitation treatments such as dietary changes, compensatory tactics, and speech therapy training are recommended in addition to immunotherapy. More intrusive methods, such as Botox injections into an overactive cricopharyngeal muscle, should be investigated further [106-108, 121].

2) Neuromyelitis Optica Spectrum Disorders (NMO-SD)

Apart from ocular neuritis and myelitis, antibodies against aquaporin 4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) [122] identify the NMO-SD. Clinical dysphagia in AQP4-NMO-SD is most commonly associated with additional symptoms including nausea, vomiting, persistent hiccups, dysarthria, or hypoglossal palsy [123, 124], although it can sometimes occur alone [125, 126]. Dysphagia is usually induced by a lesion in the brainstem or medulla oblongata, and may include the nucleus ambiguus, which is located near the region postrema and is responsible for persistent hiccups, nausea, and vomiting in AQP4 NMO-SD [126, 127]. Even with an intact blood brain barrier, the region postrema is a circumventricular area that permits entry to serum AQP4 autoantibodies [128, 129]. Medulla oblongata lesions were found in 26% of 170 NMO-SD patients (most of whom were AQP4-autoantibody positive), with 30% of them exhibiting clinical dysphagia or choking cough. Dysphagia, on the other hand, was uncommon in individuals without medulla oblongata lesions (only 1.4 %) [130, 131]. Clinical dysphagia can also develop in NMO-SD patients who are seronegative or have MOG autoantibody positivity, indicating brainstem involvement. 8 of the 13 NMO-SD patients studied with FESS had abnormalities (six had AQP4, five had MOG autoantibodies, and two were seronegative) [132]. Interestingly, six of them were clinically asymptomatic without MRI symptoms of brainstem involvement, while being classed as slightly dysphagic by FESS (relative to controls). Patients labelled as moderately or severely dysphagic by FESS, on the other hand, exhibited brainstem involvement. According to the study, subclinical dysphagia can be common in NMO-SD, presumably indicating brainstem damage not seen on MRI, as has been found before for some MS patients [124]. Patients with post-polio syndrome due to late motor neuron dysfunction in the brainstem nuclei, 20-30 years after acute paralytic poliomyelitis, have also been seen with subclinical dysphagia identified by ultrasound; of note, autoimmunity has been implicated in these patients, leading to an ongoing trial with intravenous immunoglobulin [132]. Testing for AQP4 and MOG autoantibodies can substantially contribute in the diagnosis of NMO-SD. Immediate and vigorous immunotherapy with corticosteroids, plasma exchange, or IVIg is recommended for all symptoms, including dysphagia, followed by maintenance therapy with mycophenolate [133], rituximab [134], inebilizumab [135], or eculizumab [136]. In MOG-positive patients, similar medications, such as steroids for acute relapses [137] and B-cell depletion therapy [138, 139] are used.

3) Stiff-Person Syndrome (SPS) and Glutamic acid decarboxylase (GAD)-Spectrum autoantibody associated Disorders (GAD-SD)

SPS-spectrum disorders (SPS-SD or GAD-SD) are defined by the presence of high-titer antibodies against glutamic acid decarboxylase (GAD) in the patients' serum, which also reflects intrathecal synthesis and include stiff-person syndrome, cerebellar ataxia, autoimmune epilepsy, and encephalopathy [140-142]. SPS is characterised by muscular spasms and stiffness in the trunk and proximal limbs, which frequently include the face muscles; 15% of patients also have ataxia, dysarthria, and dysphagia. Progressive Encephalopathy with Rigidity and Myoclonus (PERM) is a unique condition with muscular stiffness, spasms, myoclonus, and brainstem dysfunction, as well as oculomotor abnormalities, dysphagia, gait ataxia, substantial autonomic involvement, and anti-Glycine receptor antibodies. Anti-Glycine receptor antibodies appear to be harmful, despite the fact that GAD antibodies have not been proven to be pathogenic. [143, 144] Dysphagia can occur in both PERM and SPS, particularly when bulbar, brainstem, or cerebellar symptoms are present, as they are in at least 15% of patients [141-143]. Dysphagia may be a severe symptom, especially in patients with co-existing cerebellar ataxia, and is frequently accompanied with dysphonia, in our experience with a significant number of SPS-SD patients. Symptomatic treatments with GABA-enhancing medications, such as benzodiazepines, baclofen, or gabapentin, and immunotherapy with IVIg or rituximab, are used to treat dysphagia in SPS-SD and PERM [140]. IVIg was found to be successful in a controlled study of SPS patients and is currently the therapy of choice [145]. However, due to a high placebo effect, a controlled study with rituximab did not demonstrate statistically significant benefits, yet a minority of SPS patients saw dramatic and durable improvements [146].

4) Autoimmune Encephalitides

Dysphagia can occur in autoimmune encephalitides, albeit this link is frequently obscured by reduced level of awareness. Several acute encephalitides have been linked to clinical dysphagia, including –

(a) People who have antibodies to synaptic antigens such Anti-N-methyl-D-aspartate receptor (NMDAR) and Gamma Aminobutyric Acid Receptor B (GABAR-B).
(b) Acute disseminated encephalomyelitis (ADEM) as part of a bilateral opercular syndrome, also known as Foix-Chavany-Marie syndrome, in which face, tongue, pharyngeal, and masticatory muscular paralysis is common [147, 148];
(c) Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS) [149, 150];
(d) Autoantibody-associated disease with substantial gastrointestinal dysmotility [151]; Dipeptidyl Peptidase-like Protein-6 (DPPX)-related disease with prominent gastrointestinal dysmotility,
(e) Hashimoto encephalopathy [152];
(f) Bickerstaff brainstem encephalitis [153, 154], and
(g) The newly identified disease characterised by autoantibodies against the brain neuronal adhesion molecule IgLON5, which manifests as a bulbar syndrome with dysphagia, sleep disturbances (parasomnias, difficulty breathing), cognitive decline, and progressive supranuclear palsy-like symptoms (50-86% of cases) [155, 156].

Autoantibodies against intracellular antigens such as Hu, Ri, neurochondrin, Glial Fibrillary Acidic Protein (GFAP), Ma antigen-2 (Ma2), or Rho GTPase-activating protein 26 (Rho GTPase-activating protein 26) can cause dysphagia in several, mostly paraneoplastic, autoimmune CNS syndromes [90, 157-160]. Immunotherapy is used to treat dysphagia in all of these conditions, and its effectiveness varies.

Treatment

After the patient has been stabilised, the first and most important step is to determine whether or not the dysphagia is the result of an acute attack (the other differentials could be pseudo relapse due to infections, progression of previously encountered mild dysphagia, medication adverse events, local pathologies of the gastrointestinal tract, or another disease like Guillain-Barre syndrome, botulism, myasthenia gravis or many other diseases). Anti-inflammatory therapy for acute recurrence may be beneficial in alleviating symptoms if the relapse is confirmed. Steroids, intravenous immunoglobulins (IVIg), and plasma exchange in refractory instances are some of the therapies available. The treatment option chosen would be determined by the patient's condition, any contraindications to obtaining any of the above alternatives, and the therapy's availability. The next stage is to determine if the disease-modifying medication should be switched or begun in a patient who has not previously received treatment. Apart from the first immunological treatment, a comprehensive approach to the patients' demands is required. The matter should be discussed with neurologists, dentists, and otolaryngologists. Speech therapists and dieticians [152] may be of considerable assistance. The first efforts might include lifestyle changes (identifying the optimal head, neck, and chest posture, the most appropriate food consistency [153], and mouth cleanliness) as well as a search for potentially harmful medications. The two most researched therapies for dysphagia in MS are electrical stimulation [154, 155] and botulinum toxin injection [156]. When there are evidence of a hyperactive sphincter (cricopharyngeal muscle), botulinum toxin is appropriate [157]. To avoid any negative consequences, it should be done by expert hands [156, 158]. Although the evidence for electrical stimulation is currently lacking, some encouraging results have been seen [155, 159, 160]. This modification of central pattern generators of swallowing through vagus nerve stimulation, according to Marrosu et al., might have beneficial benefits [154]. In severe situations, a gastrostomy is the only option. More over half of MS patients who had a gastrostomy survived for two or more years following the surgery [161]. Another experimental approach with promising first outcomes is transcranial direct current stimulation [162, 163]. Cognitive rehabilitation might be a good way to deal with the challenges that come along with swallowing disorders [164].

2.Conclusion

Dysphagia is a symptom of a variety of autoimmune neurological illnesses that affect the entire neuraxis (muscles, neuromuscular junctions, nerves, roots, brainstem, and cortical areas), and can occur alone or in conjunction with other symptoms. Early recognition of the underlying reasons and clinical manifestations of autoimmune neurogenic dysphagia is critical since immunotherapy can be successful in reducing dysphagic symptoms if started promptly. Dysphagia can appear insidiously in the context of an autoimmune neurological illness, but it can also appear abruptly or subacutely as the first symptom of a developing neuro-autoimmunity. Dysphagia is more frequent in inflammatory myopathies, although it can also occur in DM, anti-SS-OM, and NAM/IMNM; an increased CK raises suspicion, and a muscle biopsy confirms the diagnosis. Despite the fact that immunotherapy is often successful, IBM is still a tough disease to treat. Dysphagia is frequently related with fatigability and other cranial nerve dysfunction in MG, and it responds well to immunotherapy when the diagnosis is confirmed by the identification of particular autoantibodies. Acute dysphagia, such as that seen in PCB, MFS, and GBS variants, should be recognised and treated early to improve outcomes; more insidious dysphagia is seen in paraneoplastic neuropathies, highlighted by anti-Hu/-Ri autoantibodies, and in ganglionopathies associated with autonomic dysfunction, gastrointestinal dysmotility, and antibodies to gAChR or VGCC. Autoimmune hyperexcitability diseases, such as SPS-SDs, which are characterised by hyperexcitability, spasms, and high-titer anti-GAD autoantibodies, are under-appreciated causes of possibly curable autoimmune dysphagia. Given the wide range of neurological autoimmune illnesses and disease

mimics that cause dysphagia, increasing knowledge is essential for establishing the accurate diagnosis and initiating immunotherapy, as the majority of the underlying neurological disorders are potentially curable.

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